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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/309,038	05/10/1999	PETER BERNARD HEIFETZ	A-30496B	7012

22847 7590 08/12/2003

SYNGENTA BIOTECHNOLOGY, INC.
PATENT DEPARTMENT
3054 CORNWALLIS ROAD
P.O. BOX 12257
RESEARCH TRIANGLE PARK, NC 27709-2257

EXAMINER	
MEHTA, ASHWIN D	
ART UNIT	**PAPER NUMBER**
1638	22

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/309,038	HEIFETZ ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12,16-30,34-40,46,47,49,50,52,56-58,60,62,73 and 76-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-12,16-30,34-40,46,47,49,50,52,56-58,60,62,73 and 76-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has b1een withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 November 2002 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 56-58, 60, and 61 under 35 U.S.C. 112, 2nd paragraph, is withdrawn, in light of the claim amendments and cancellations.

4. The rejection of claims 1-30, 33-40, 46-52, 56-65, 70, and 73-75 under 35 U.S.C. 103(a) is withdrawn and replaced with the rejection below.

Claim Objections

5. Claim 46 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

claim(s) in independent form. The claim limits that cell of claim 52 by requiring the expression of said vial genome or portion thereof in said cell to be reduced. However, the method of parent claim 1 indicates this.

Claim Rejections - 35 USC § 112

6. Claims 1, 4-12, 16-30, 34-40, 46, 47, 49, 50, 52, 56-58, 60, 62, and 73 remain and new claims 76-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the Office action mailed 25 June 2002 under item 5. Applicants traverse in the paper submitted 25 November 2002. Applicants' arguments were fully considered but were not found persuasive.

Applicants argue that the specification describes use of the present methods to produce plants that have resistance to a furovirus, and use of a 452 bp portion of a furovirus replicase to achieve virus resistance. Applicants argue that one or more declarations will be provided on resistance to tospovirususes, potyviruses, and cucomoviruses (response, page 4, 6th full paragraph).

However, the sequence of the BNYVV RNA 1 is not provided. Example 9 on page 42 indicates that the sequence can be found in "accession number DO0115". However, the database that contains this number is unknown. For example, it is not a GenBank accession number.

Further, the claims still broadly encompass all portion sizes of the viral genomes in the claimed methods and products. The smallest size fragment that Applicants describe that conferred increased resistance viral resistance (to BNYVV) in plants is a 452 nucleotide fragment from the BNYVV replicase gene (Example 9; declaration submitted 19 June 2001). The specification does not describe any viral genome portions smaller 452 nucleotides that conferred viral resistance to plant cells with the claimed method. Voinnet (Trends in Genetics, 2001, Vol. 17, pages 449-459) teaches that 21-23 nt. long RNAs are formed from the targeted transcript during RNA silencing in virus-infected plant cells (page 451). The specification has not described any viral genome portions smaller than 21 nt. that can be used with the claimed invention, as encompassed by the claims.

7. Claims 1, 4-12, 16-30, 34-40, 46, 47, 49, 50, 52, 56-58, 60, 62, and 73 remain and new claims 76-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record stated in the Office action mailed 25 June 2002 under item 6. Applicants traverse in the paper submitted 25 November 2002. Applicants' arguments were fully considered but were not found persuasive.

Applicants argue, regarding viral genomes that express PTGS suppressors, that data will be provided in future declarations showing use of the method described in the present

specification to obtain plants resistant to viruses known to encode suppressors (response, page 5, 7th paragraph). Applicants' intention is acknowledged.

Applicants did not address the issue concerning the lack of enablement for the portion of a viral genome that can be used with the claimed invention. Further, the specification indicates that the fragment of the BNYVV replicase gene that is taught in Example 9 is 452 bp long and is found between nucleotides 5168-5620, in relation to the sequence of BNYVV RNA1. The specification on page 42 indicates that this nucleotide sequence is in relation to the BNYVV RNA1 sequence in "accession no. DO0115" (1st full paragraph). However, the specification does not indicate the database that contains this accession number. As the reference sequence is unknown, the sequence from "5168-5620" of the BNYVV replicase gene (RNA1) is not taught. The specification also does not teach any other fragment of BNYVV that is about 400 nucleotides that can be used with the claimed invention to cause a reduction in expression of a viral genome in plant cells. As discussed above, Voinnet teaches that 21-23 nt. long RNAs are formed from the targeted transcript during RNA silencing in virus-infected plant cells. It is not clear how portions of viral genomes that are smaller than 21 nt. can be used with the claimed invention. Further, Peele et al. (Plant J., 2001, Vol. 27, pages 357-366) teach that a 51-bp fragment of the tobacco su gene, when expressed in Nicotiana benthamiana, was near the threshold for effective silencing, while noting that smaller fragments of the green fluorescent protein gene were sufficient to cause silencing of that gene in plants. Peele et al. assert that genes may have different size requirements to obtain silencing (page 364). It is not clear, in the absence of further guidance, what portions of the furovirus, potyvirus, tospovirus, and cucomovirus genomes can be used with the claimed invention.

8. Claims 81 and 82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn towards a method of conferring resistance or tolerance to furovirus, potyvirus, tospovirus, or cucomovirus upon a plant cell, comprising introducing into a plant cell a first DNA sequence capable of expressing in said cell a sense RNA fragment of a furovirus, potyvirus, tospovirus, or cucomovirus genome or portion thereof and a second DNA sequence capable of expressing in said cell an antisense RNA fragment of said furovirus, potyvirus, cucomovirus, or tospovirus genome or portion thereof, wherein said RNA fragments form a double-stranded RNA molecule, and wherein the expression of said viral genome or portion thereof is said cell is reduced, wherein the portions are from the replicase gene of BNYVV and are about 400 nucleotides or are from about nucleotide 5178 to about nucleotide 5620.

The specification in Example 9 indicates that a chimeric gene cassette was constructed, encoding sense and antisense RNA fragments from nucleotides 5168-5620 of BNYVV RNA 1, which is the replicase gene. However, the specification does not describe the claimed method wherein the portion of the replicase gene from BNYVV is "about 400 nucleotides" or from "about" nucleotide 5178 to "about" 5620. These recitations in claims 81 and 82 constitute NEW MATTER, and must be removed.

9. Claims 1, 4-12, 16-30, 34-40, 46, 47, 49, 50, 52, 56-58, 60, 62, 73, and 76-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite because it is dependent on cancelled claim 2.

In claims 1 and 12: the claims are indefinite because their preambles are not consistent with the last recited method steps. Both claimed methods are for conferring resistance or tolerance to a furovirus, potyvirus, tospovirus, or cucomovirus upon a plant cell. However, the last recited step in both claims results in reduction of expression of a viral genome or portion thereof in a plant cell, which does not have to yield a virus resistant or tolerant plant cell. It is suggested that the claims be amended by adding, in the last line after "reduced," the recitation, --and said plant cell has resistance or tolerance to said furovirus, potyvirus, tospovirus, or cucomovirus--.

Further in claim 12: the recitation, "capable of expressing" in lines 3 and 5 renders the claim indefinite. The recitation does not make clear if the sense and antisense fragments are actually expressed, or when or under what conditions the fragments are expressed. It is suggested that the recitations, "capable of expressing in said cell" be replaced with --encoding--, and that the recitation, --when expressed in a plant cell--, be inserted in line 7 after "molecule".

In claims 5, 16, 56, 58, 77, 79, and 83-85: the recitation, "derived" renders the claims indefinite. It is not clear what the nucleotides sequences are, as it is not clear how they were derived. It is not clear what the plant or progeny of claim 56 are, as it is not clear how they were derived. It is not clear what is encompassed by "derived." The metes and bounds of the claims

are unclear. It is suggested that the recitation be removed from claims 5, 16, 58, 77, 79, and 83-85. In claim 56, it is suggested that the recitation be replaced with, --regenerated--.

Further in claim 56: the recitation, "A plant and progeny thereof derived from the plant cell" renders the claim indefinite. The claim can be read to indicate that the progeny is derived directly from the plant cell. It is suggested that the recitation directed to the progeny be removed, and a new claim be introduced directed to the progeny of the plant, wherein the plant is resistant or tolerant to the virus and its genome comprises the first and second DNA sequences.

In claim 58: the claim is indefinite because it is not clear if the seeds are from the plant or progeny.

In claims 46, 49, 52, 56, 58, 62, 73, and 76 are indefinite, because it is not clear if the claims cells, plants, and seeds are virus resistant. It is suggested that the claims be amended to indicate that the claimed products have resistance or tolerance to the virus that comprises the RNA fragment in its genome, as this is the invention.

In claim 47, 50, 57, and 60: the recitation, "said cell (or plant) is virus resistant or tolerant" renders the claims indefinite, for broadening the scope of the claims from which they depend. The claims broadly encompass resistance or tolerance to any virus. However, their parent claims are directed to methods for conferring resistance or tolerance to a furovirus, potyvirus, tospovirus, or cucomovirus.

In claim 62: there is improper antecedent basis for the recitation, "the two RNA sequences of claim 8". Claim 8 is directed to a method, not RNA sequences.

Claim Rejections - 35 USC § 103

10. Claims 1, 4-12, 16-30, 34-40, 46, 47, 49, 50, 52, 56-60, 62, 73, and 76-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (U.S. Patent No. 6,506,559) in combination with de Haan et al. (J. Gen. Virol., 1991, Vol. 71, pages 2207-2216), Maiss et al. (J. Gen. Virol., 1989, Vol. 70, pages 513-524), Saito et al. (Arch. Virol., 1996, Vol. 141, pages 2163-2175), Hsu et al. (Arch. Virol., 1995, Vol. 140, pages 1841-1847), Miki et al. (Procedures for Introducing Foreign DNA into Plants, In Methods in Plant Molecular Biology and Biotechnology, 1993, Bernard R. Glick and John E. Thompson, Eds., CRC Press, Inc., Boca Raton, FL), Applicants' admitted state of the prior art, and Keddie et al. (Plant Mol. Biol., 1994, Vol. 24, pages 327-340).

The claims are broadly drawn towards a method for conferring resistance or tolerance to any furovirus, potyvirus, tospovirus, or cucomovirus upon any plant cell, comprising introducing into a plant cell a sense RNA fragment of a viral genome or portion thereof and an antisense RNA fragment of said viral genome or portion thereof, wherein said fragments form a double-stranded molecule and wherein expression of said viral genome or portion thereof in said cell is reduced; or wherein the RNA fragments are in two different molecules, or mixed before introduction into the cell, or introduced sequentially into the cell, or are comprised in the same RNA molecule; or said method wherein the RNA fragments are expressed from DNA; a plant cell obtained from said method; a plant obtained from said cell; seed derived from said plant.

Fire et al. teach a method to inhibit expression of a target gene in a cell comprising formation of a double-stranded RNA in a cell, wherein one strand of the RNA corresponds to a nucleotide sequence found within a target gene and wherein the second strand is complementary

to the first strand, and the double stranded RNA inhibits expression of the target gene. The cell types comprising the target gene include plant cells. The target gene may be a gene from a pathogen that is capable of infecting the cell, including viruses. A single, self-complementary RNA, or two complementary RNA strands may form the double-stranded RNA. RNA duplex formation may be initiated either inside or outside the cell. The RNA strands may also be transcribed inside the cell from transgenes comprising regulatory regions, which include promoters and splice donor and acceptors. The lengths of the RNA fragments that can be used include those that are 400 bases (col. 4, line 20 to col. 5, line 3; col. 6, lines 44-49; col. 8, lines 4-5; col. 10, lines 8-9; col. 11, lines 37-40; claims).

Fire et al. do not teach plant virus sequences, or tissue-specific, developmentally regulated, inducible, or bi-directional promoters.

de Haan et al. teach nucleotide sequence of the L RNA of the tomato spotted wilt virus (TSWV), and assert that this virus is a member of the tospovirus genus of the Bunyaviradae, which infect plants (pages 2207-2211, 2215).

Maiss et al. teach the nucleotide sequence of the plum pox virus (PPV), a member of the potyvirus group, and assert that it causes heavy yield losses in plum, peach, and apricot (pages 513, 515-523).

Saito et al. teach the nucleotide sequence of the Japanese isolate S of beet necrotic yellow vein virus (BNYVV), and assert that this virus is responsible for rhizomania disease of sugar beet, and that RNA1 encodes functions required for viral RNA replication (page 2163, 2165-2173).

Hsu et al. teach the nucleotide sequence of the cucumber mosaic virus (CMV) and assert that it is one of the most widespread plant viruses infecting 775 plant species, including both monocots and dicots (pages 1841-1846).

Miki et al. teach Agrobacterium- and microprojectile-mediated methods to stably transform plants (pages 67-83).

Applicant's specification admits that the prior art teaches plant tissue specific, developmentally regulated and inducible promoters, use of intron sequences, and methods to introduce RNA into plant cells (pages 13, 20-22).

Keddie et al. teach a plant bi-directional promoter (pages 332-338). This reference is cited to address the limitation of bi-directional promoters.

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to use the method of inhibiting expression of a target gene of Fire et al. to introduce into plant cells, a sense RNA fragment of a plant virus, and its complementary sequence, or DNA encoding said RNA, such that the two RNA fragments form a double stranded RNA molecule in the cell, and inhibit expression of a gene expressed by the virus, when that virus infects the cell. It would have been obvious that such inhibition would have increased the resistance or tolerance of the plant cell to that plant virus. It would have been obvious to stably transform a plant cell with a DNA construct that comprises DNA sequences encoding sense and antisense RNA fragments from a viral gene of any plant virus, including a fragment from the TSWV, PPV, BNYVV, and CMV genomes, taught by de Haan et al., Maiss et al., Saito et al., and Hsu et al., respectively, operably linking the nucleotide fragments to promoters such that sense- and anti-sense RNA fragments get expressed and form a dsRNA molecule. Any

appropriate plant transformation method could have been used, including those taught by Miki et al. It was obvious that the RNA fragment could have been from viral genes required for infection, such as genes required for viral RNA replication, for example sequences 5278-5620 of BNYVV RNA-1. As Saito et al. assert, BNYVV RNA1 contains sequences needed for viral replication. As taught by Fire et al., the dsRNA inhibits expression of the target gene from which the sequences were taken. Fire et al. teach that a single, self-complementary RNA, or two complementary RNA strands could have formed the double-stranded RNA. Therefore it was obvious that the two sequences could have been encoded by the same strand of DNA in the DNA construct, or on complementary strands, or on different DNA constructs that get co-transformed into the cell. It was obvious that the sense- and anti-sense-encoding DNA sequences could have been operably linked to any of a variety of different constitutive, developmentally-regulated, inducible, or tissue-specific promoters, depending on one's desired end. These promoters were taught in the art, as admitted in Applicants' specification. One could also have used a bi-directional promoter, such as that taught by Keddie et al. Whether the two promoters regulating the two sequences were of the same type or different was a matter of choice. The sense-and anti-sense encoding DNA sequences could also have been operably linked to the same promoter and been transcribed into a single RNA molecule, in which case a linker sequence obviously would have been placed in between the two sequences so that steric hindrance would not have prevented the expressed RNA from forming a double-stranded molecule. The linker sequence could also have included an intron, such as that taught by Applicants' admitted state of the prior art. It would also have been obvious to collect seed from the transgenic plants for the purpose of propagation, to produce progeny that have inherited the DNA encoding the RNA fragments,

thereby inheriting the viral resistance or tolerance. The sense- and anti-sense RNA fragments themselves could also have been introduced into cells of a plant directly, as taught by Fire et al. Many obvious variations on this theme would also have worked, as long as the sense- and anti-sense RNA sequences of the target gene were present so that they formed a dsRNA molecule in the plant cell. That is, the sense- and anti-sense RNA sequences could also have been on the same molecule, on two different RNA molecules, mixed before introduction into the cell, or introduced sequentially, since the important aspect is dsRNA formation. One would have been motivated to prevent replication of TSWV, PPV, CMV, or BBYV in plant cells and plants, given that these viruses were known plant pathogens.

11. No claim is allowed.

Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta, whose telephone number is 703-306-4540. The examiner can normally be reached on Mondays-Thursdays and alternate Fridays from 8:00 A.M to 5:30 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 and 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general

nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ashwin D. Mehta, Ph.D.
Primary Examiner
Art Unit 1638